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Quasi-Experimental Study of Sodium Citrate Locks and the Risk of Acute Hemodialysis Catheter Infection among Critically Ill Patients

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Critically ill patients who require renal replacement therapy (RRT) are vulnerable to catheter-related bloodstream infections (CRBSI). This study compared the risks of dialysis catheter infection according to the choice of locking solution in the intensive care unit (ICU). A prospective quasi-experimental study with marginal structural models (MSM) and 2:1 greedy propensity-score matching (PSM) was conducted at nine university-affiliated hospitals and three general hospitals. A total of 596 critically ill patients received either saline solution or heparin lock solution (the standard of care [SOC]) from 2004 to 2007 in the Cathedia cohort ($n = 464$ for MSM; $n = 124$ for PSM) or 46.7% citrate lock from 2011 to 2012 in the citrate (CLock) cohort ($n = 132$ for MSM; $n = 62$ for PSM) to perform RRT using intermittent hemodialysis. Catheter-tip colonization and CRBSI were analyzed. The mean duration (standard deviation [SD]) of catheterization was 7.1 days (6.1) in the SOC group and 7.0 days (5.9) in the CLock group ($P = 0.84$). The risk of dialysis catheter-tip colonization was lower in the CLock group (20.5 versus 38.7 per 1,000 catheter-days in the SOC group; hazard ratio [HR] from MSM, 0.73; 95% confidence interval [CI], 0.57 to 0.93; $P < 0.02$). Consistent findings were found from PSM (HR, 0.46; 95% CI, 0.22 to 0.95; $P < 0.04$). The risk of CRBSI was nonsignificantly different in the CLock group (1.1 versus 1.8 per 1,000 catheter-days in the SOC group; HR from MSM, 0.48; 95% CI, 0.12 to 1.87; $P = 0.29$). By reducing the risk of catheter-tip colonization, citrate lock has the potential to improve hemodialysis safety in the ICU. Additional studies are warranted before the routine use of citrate locks can be recommended in the ICU.

Critically ill patients with acute kidney injury (AKI) who require renal replacement therapy (RRT) are particularly vulnerable to nosocomial infections (1, 2). Therefore, any improvement in catheter management strategies that could delay the risk of catheter-related bloodstream infection (CRBSI) has the potential to improve patient safety (3) and reduce costs (4).

An increased understanding of the role of biofilms has added an exciting dimension and a significant challenge to device-related infection prevention. Compared with the central venous catheters used for the administration of medications, a unique feature of hemodialysis catheters is their intermittent use. In a pilot ($n = 78$) open-label, single-center, randomized controlled trial among critically ill patients requiring RRT, Hermite et al. (5) reported a significantly longer time for central catheter-associated bloodstream infection (CLABSI) (6) to occur in the citrate locking group (20 days versus 14 days in the saline solution locking group; hazard ratio [HR], 2.8; 95% confidence interval [CI], 1.0 to 7.6; $P = 0.04$). Of note, the incidence of CLABSI in this study (5) was >24 per 1,000 catheter-days and contrasts with the incidence of CRBSI found in the multicenter Cathedia cohort (1.9 per 1,000 catheter-days) (7) and in the study by Skofic et al. (8) conducted using the same type of patients (1.6 per 1,000 catheter-days). Whether citrate lock is more effective than saline solution or heparin lock in intensive care unit (ICU) settings and whether it is associated with a lower incidence of CRBSI remain unclear (9).

We hypothesized that the risk of dialysis catheter infection would be lower with the use of sodium citrate locks in the ICU. This study aimed to compare the risks of catheter-tip colonization at the time of catheter removal among patients requiring RRT according to a protocol using sodium citrate locks (CLocks) versus saline solution or heparin lock solution (the standard of care [SOC]) during the interdialytic period. Secondary endpoints were catheter dysfunction, duration of catheterization, CRBSI, and ICU mortality.

MATERIALS AND METHODS

Study design, setting, and population. The CLocks was a retrospective, quasi-experimental, cohort study conducted at Caen University Hospital that enrolled all consecutive patients admitted to the ICU who required RRT between January 2011 and December 2012. Data were prospectively collected as a part of the French REA-Raisin surveillance network, which targets device-associated infections. Only adults who were undergoing their first temporary 2-lumen, 14-French (Fr), nontunneled, venous catheterization for intermittent hemodialysis (Arrow International, PA) were included in the study.

To serve as controls, we used the patients included in the Cathedia study, which was a multicenter study involving the Caen University Hospital in addition to 8 university hospitals and 3 general hospitals. The comparison of a group of patients admitted to a single institution with a group of patients admitted to the same institution plus 11 other institu-

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tions cannot adjust for a possible center effect. Therefore, we also conducted a sensitivity analysis by restricting the control group to patients admitted to the Caen University hospital. The study was approved by the institutional review board (IRB) of the Côte de Nacre University Hospital. Informed written consent was obtained from all of the participants or their proxies. Given the retrospective and quasi-experimental nature of this analysis, no additional IRB approval was requested. Details of the dialysis catheters used in the Cathedia study were described elsewhere (7) and were consistent with those used in the CLock study. For the present analysis, we excluded patients who exclusively received continuous RRT and catheters that were not inserted first in the ICU (10).

Catheter insertion and care. Dialysis catheters were not used for drug administration, and only jugular and femoral sites were used. All of the protocols used in this study to prevent catheter infection, including the use of masks, caps, gowns, sterile gloves, sterile drapes, and catheter hub disinfection, were standardized and followed the Centers for Disease Control recommendations (CDC) and French recommendations (11). We used 5% povidone iodine–70% ethanol (Betadine Alcoolique; MEDA Pharma, Mérignac, France) after scrubbing the insertion site with a 4% povidone iodine detergent (Betadine Scrub; MEDA Pharma, Mérignac, France) for all dialysis catheters used in the study (12). Catheter care maintenance, including cleaning the catheter hubs, used 5% povidone iodine–70% ethanol (Betadine Alcoolique; MEDA Pharma, Mérignac, France). In the Cathedia and CLock cohorts, all dialysis catheters were aseptically removed and systematically sent to culture, regardless of the clinical patients' statuses. Catheter colonization, as defined below, was the primary endpoint in the original Cathedia trial and an item of the French REA-Raisin surveillance network in the CLock cohort.

Protocol for hemodialysis catheter maintenance. (i) Catheter lock with sodium citrate. In the CLock group, the locks were made by injecting 10 ml of saline solution and subsequently filling each branch of the catheter with citrate solution (DuraLock-C [46.7%]) according to the recommendation of the manufacturer (*med*COMP, Harleysville, PA). Once the citrate locks were in place, catheter manipulation was forbidden until the next dialysis session, and the citrate lock was removed by aspiration before the next dialysis session in an attempt to minimize release of the solution into systemic circulation.

(ii) Standard of care. Only SOCs were used to lock the dialysis catheter in the Cathedia cohort according to the practice of each center.

Endpoints. (i) Catheter-tip colonization. The primary endpoint of this study was catheter-tip colonization, defined as cultures with $\geq 10^3$ CFU per millimeter of growth, according to the Brun-Buisson vortex technique without neutralizing broth (7).

(ii) Catheter dysfunction. Catheter dysfunction, which served as the secondary endpoint in the Cathedia trial (13), was similarly defined as an inability to attain an adequate blood flow, requiring catheter replacement.

(iii) Other endpoints. We also compared the durations of catheterization in days from the time of insertion to removal, the CRBSI incidence, and all-cause ICU mortality. CRBSI was defined as catheter-tip colonization with one concordant peripheral blood culture for pathogens and two concordant peripheral blood cultures for potential skin contaminants.

Power and statistical analysis. The catheter-tip colonization rate in the Cathedia cohort was 24% (7). We expected a 50% reduction in the rate of catheter-tip colonization (primary endpoint) with citrate lock. Considering a two-sided alpha risk of 5% and a sample size ratio of 4 between groups (Cathedia/CLock), a total of 103 patients in the CLock group (and 412 controls) were required to provide a statistical power of 80%.

The data were expressed as the means ± standard deviations (SD) or medians (interquartile range) and percentages, depending on the nature of the variable of interest. The incidence densities were expressed as the number of events divided by the number of catheter-days. We used propensity-score methods, namely, marginal structural models (MSM) and 2:1 greedy propensity-score matching (PSM), to ensure that the Cathedia and Clocks populations were comparable. The addition of risk factors to the MSM and the PSM model revealed consistent results and thus was not shown. A hazard ratio of <1 corresponded to a protective effect of CLock compared to the SOC. In addition, MSM was used in a sensitivity analysis by restricting the Cathedia cohort to the patients admitted to the Caen University hospital only (the same institution as in the CLock cohort). We considered that a 10% change in the effect size for the primary endpoint would denote significant confounding compared to the full Cathedia sample.

A P value < 0.05 was considered to be significant, and all P values were two-tailed without adjusting for multiple comparisons. The statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline characteristics. After excluding patients who never received intermittent hemodialysis, 596 consecutive patients fulfilled the inclusion criteria and were enrolled in the Cathedia-CLock study. Among these patients, 464 (77.8%) received SOC for dialysis catheter maintenance (saline solution, 34%; heparin, 66%) and 132 (22.1%) received CLocks for dialysis catheter maintenance. In the Cathedia cohort, 127/464 (27%) patients were included at the same institution as the CLock cohort ($n = 132$). The baseline characteristics of the two cohorts are reported in Table 1, which shows significant differences between the two groups. Regarding predictors of catheter-tip colonization (Table 1), antibiotic treatment (protective), hypertension (risk factor), and diabetes (risk factor) were more frequent in the CLock group than in the SOC group.

Unadjusted analyses. Among the 464 patients who received SOC, the overall cumulative incidence of catheter colonization was 27.6%, which corresponded to an incidence density of 38.7 per 1,000 catheter-days (95% CI, 27.7 to 52.2). Among the 132 patients who received CLock, the overall cumulative incidence of catheter colonization was 14.4%, which corresponded to an incidence density of 20.5 per 1,000 catheter-days (95% CI, 13.0 to 30.9). The time to colonization at the time of catheter removal was significantly longer (Fig. 1A) in the CLock group than in the SOC group (HR, 0.53; 95% CI, 0.33 to 0.87; $P < 0.02$).

The microbiological findings of catheter-tip colonization are shown in Table 2. Among the cases of colonization, the distributions of Gram-positive bacteria, Gram-negative bacteria, fungi, and polymicrobes were homogeneous between groups ($P = 0.40$). The distributions of Gram-positive bacteria differed between groups ($P < 0.02$), with a higher incidence of catheter-tip colonization of *Staphylococcus epidermidis* in the SOC group than in the CLocks group.

As shown in Fig. 1B, more dialysis catheters were removed due to dysfunction in the SOC group (46 [9.9%] of 464) than in the CLock group (4 [3.0%] of 132), which corresponded to a significantly longer time to dysfunction in the CLock group (HR, 0.31; 95% CI, 0.11 to 0.87; $P < 0.03$).

The mean durations (SD) of catheterization were similar ($P = 0.84$) between the CLock (7.0 days [5.9]) and SOC (7.1 days [6.1]) groups (Table 1).

The overall cumulative incidences of CRBSI (Table 2) were 6 (1.3%) of 464 in the SOC group (1.8 per 1,000 catheter-days) and 1 (0.8%) of 132 in the CLock group (1.1 per 1,000 catheter-days) and did not significantly differ with respect to the catheter maintenance protocol (unweighted HR, 0.60; 95% CI, 0.07 to 4.95; $P = 0.64$). In the ICU, the mortality rates were similar between groups (Table 1).

Propensity-score analyses. The time to colonization at the

TABLE 1 Baseline and follow-up characteristics according to the hemodialysis catheter maintenance protocol before and after propensity-score matching[a]

Patient characteristic	Values for overall cohort before matching			Values for overall cohort after 2:1 propensity matching[c]	
	Cathedia ($n = 464$)	Citrate lock ($n = 132$)	P	Cathedia ($n = 124$)	Citrate lock ($n = 62$)
Baseline					
Age in years, mean (SD)	65.0 (14.9)	62.3 (13.2)	0.06[b]	60.7 (15.7)	63.1 (14.9)
No. (SD) of males	318 (68.5)	84 (63.6)	0.29[b]	82 (66.1)	43 (69.3)
BMI, mean (SD)	26.9 (5.3)	29.4 (8.4)	<0.001[b]	27.5 (5.5)	26.9 (6.4)
APACHE II score, mean (SD)	26.5 (9.0)	30.7 (10.1)	<0.001[b]	26.9 (8.6)	27.0 (7.9)
Antibiotic use, *n* (%)	273 (58.8)	94 (71.2)	0.01[b]	75 (60.5)	36 (58.1)
Immunodepression, *n* (%)	82 (17.7)	18 (13.6)	0.28[b]	15 (12.1)	7 (11.3)
Diabetes, *n* (%)	127 (27.3)	61 (46.2)	<0.001[b]	32 (25.8)	19 (30.6)
Hypertension, *n* (%)	235 (46.2)	82 (62.1)	0.03[b]	63 (50.8)	33 (53.2)
Jugular route, *n* (%)	226 (48.7)	52 (39.4)	0.06[b]	52 (41.9)	27 (43.5)
Started with CRRT, *n* (%)	91 (19.6)	52 (39.4)	<0.001[b]	32 (25.8)	14 (22.6)
Propensity to receive SOC, mean (SD)	0.815 (0.150)	0.615 (0.193)	<0.001	0.797 (0.094)	0.797 (0.096)
Follow-up					
Duration of catheterization in days, mean (SD)	7.1 (6.1)	7.0 (5.9)	0.84	8.0 (7.1)	7.5 (7.3)
Catheter colonization, *n* (%)	128 (27.6)	19 (14.4)	0.002	42 (33.9)	10 (16.1)
Catheter dysfunction, *n* (%)	46 (9.9)	4 (3.0)	0.02	6 (4.8)	2 (3.2)
CRBSI, *n* (%)	6 (1.3)	1 (0.8)	0.53	1 (0.8)	1 (1.6)
ICU mortality, *n* (%)	188 (40.5)	45 (34.1)	0.18	49 (39.5)	18 (29.3)

[a] Abbreviations: APACHE II, acute physiology and chronic health evaluation II score; SD, standard deviation; BMI, body mass index; CRBSI, catheter-related bloodstream infection; CRRT, continuous renal replacement therapy; SOC, standard of care (saline or heparinized locks).
[b] Included in the computation of the propensity score.
[c] The standardized difference between groups was <10% for all baseline characteristics after propensity-score matching.

time of catheter removal was significantly longer in the CLock group based on inverse probability weighting (weighted HR, 0.73; 95% CI, 0.57 to 0.93; $P < 0.02$). In the sensitivity analysis, restricting the control group to patients from Caen University hospital ($n = 127$), the time to colonization at the time of catheter removal was nonsignificantly longer in the CLock group based on inverse probability weighting (weighted HR, 0.76; 95% CI, 0.50 to 1.15; $P = 0.20$), corresponding to an effect size modification of 4% compared to the full control group sample. As shown in Fig. 2A, in the propensity-matched subgroup ($n = 186$), the risk for colonization at the time of catheter removal was significantly higher in the SOC group (42.6 per 1,000 catheter-days versus 21.6 in the CLock group; HR, 0.46; 95% CI, 0.22 to 0.95; $P = 0.04$).

The time to dysfunction was also significantly longer in the CLock group based on inverse probability weighting (weighted HR, 0.29; 95% CI, 0.16 to 0.51; $P < 0.001$). As shown in Fig. 2B, in the propensity-matched subgroup ($n = 186$), the time to dysfunction was not significantly higher in the SOC group (6.1 per 1,000 catheter-days versus 4.3 in the CLock group; HR, 0.78; 95% CI, 0.16 to 3.86; $P = 0.76$). Finally, the time to CRBSI in the CLock group was nonsignificantly different from that in the SOC group

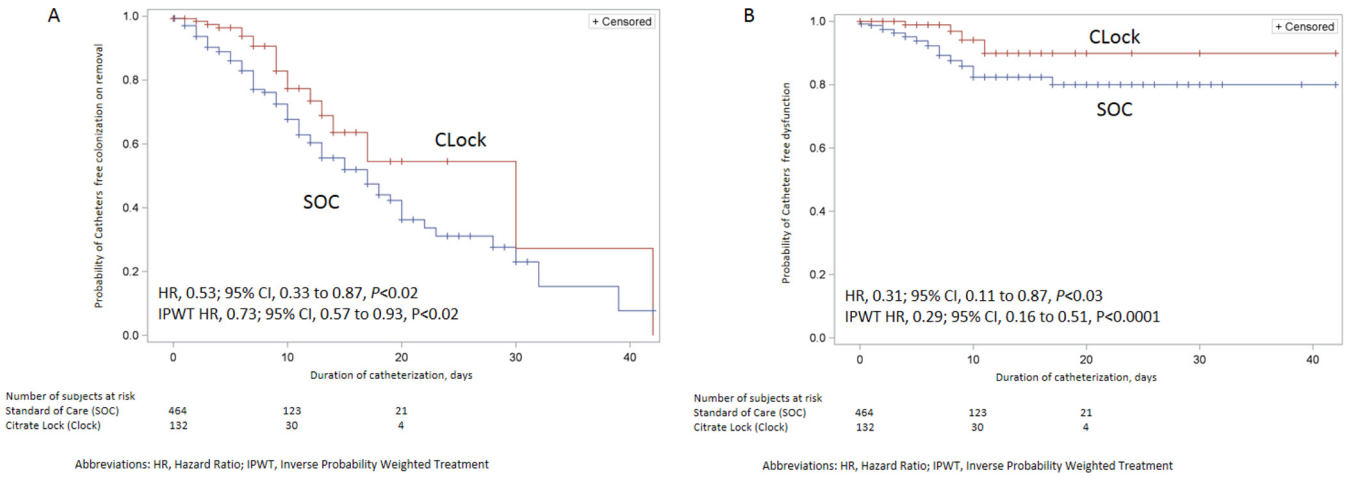

FIG 1 Kaplan-Meier curves of time to catheter colonization at the time of catheter removal (A) and at the time of dysfunction (B) in the overall cohort ($n = 596$). IPWT, inverse probability weighting.

TABLE 2 Microbiological findings

Characteristic	Value(s)			
	Overall (n = 596)	SOC (n = 464)	CLock (n = 132)	P
Catheter colonization				
n (%)	147 (25.7)	128 (27.6)	19 (14.4)	
Incidence per 1,000 catheter-days	34.7	38.7	20.5	<0.012
Microorganisms from colonized catheters, n				
Gram-positive bacteria	94	80	14	—[b]
Staphylococcus epidermidis	72	62	6	—[a]
Other	7	18	8	—[a]
Gram-negative bacteria	34	31	3	—[b]
Escherichia coli	10	9	1	
Pseudomonas aeruginosa	9	9	0	
Enterobacter spp.	6	6	0	
Other	6	7	2	
Fungi	10	10	0	—[b]
Polymicrobes	9	7	2	—[b]
CRBSI				
n (%)	7 (1.2)	6 (1.3)	1 (0.8)	
Per 1,000 catheter-days	1.6	1.8	1.1	0.64
Microorganisms from CRBSI, n				
Staphylococcus epidermidis	3	3	0	
Staphylococcus aureus	4	3	1	

[a] —, $P < 0.02$.
[b] —, $P = 0.40$.

based on probability weighting (weighted HR, 0.48; 95% CI, 0.12 to 1.87; $P = 0.29$).

DISCUSSION

Consistent with our hypothesis, the risk of dialysis catheter infection was lower with the use of sodium citrate locks in the ICU. However, the lower risk of catheter-tip colonization (38.7 versus 20.5 per 1,000 catheter-days) did not translate to a significantly lower risk of CRBSI (1.8 versus 1.1 per 1,000 catheter-days), possibly due to the low number of events expected with such a short indwell time. Our results support the concept of an antimicrobial catheter lock solution (14), specifically, a citrate solution, to prevent the risk of short-term catheter-associated infection risk among patients who require RRT in an ICU setting (5, 8).

The catheterization duration (7 days) reported in this study was similar to those reported in previous studies (5, 8, 15–18), ranging from 4.2 days (16) to 12.0 days (5). This short-term indwelling duration suggests that the extraluminal route of catheter-tip colonization predominated (19). Because filling the dialysis catheter with citrate solution can prevent only intraluminal colonization, it is unclear why we observed a significant reduction of

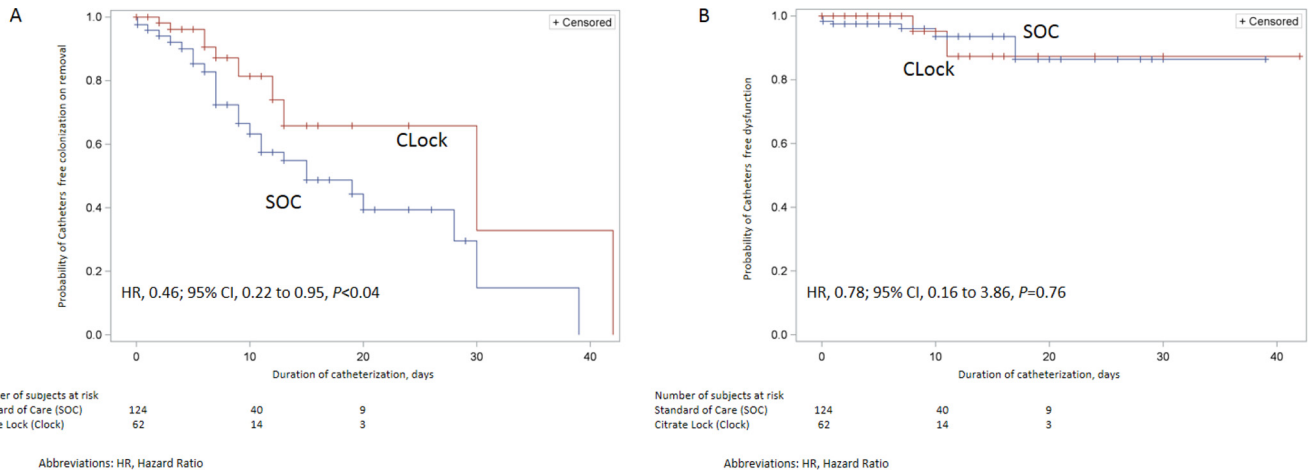

FIG 2 Kaplan-Meier curves of time to catheter colonization at the time of catheter removal (A) and at the time of dysfunction (B) after propensity-score matching (n = 186).

catheter-tip colonization in our study. The first hypothesis is that, similarly to long-term dialysis catheters (20, 21), the intraluminal route of catheter-tip colonization may predominate for short-term dialysis catheters in the ICU population due to frequent manipulations of the catheter hub or connectors and possibly the choice of the locking solution (22). Additional studies on the dynamics of catheter colonization are warranted in this setting. However, the use of ethanol lock in the ICU did not reduce the risk of the use of a dialysis catheter (NCT00875069). The second hypothesis is that spillage of the locking solution around the intravascular catheter tip also affects extraluminal catheter-tip colonization (23), despite a lower citrate concentration at the catheter tip (24). Even when the appropriate fill volume is used, laminar flow results in the injected catheter lock solution streaming down the center of the lumen and the citrate solution spilling into the bloodstream (25). This finding also supports the close monitoring of the calcium plasma level, even when citrate is used as a catheter locking solution.

Our ICU chose to utilize a 46.7% citrate lock solution because this medical device (DuraLock-C) was already approved as a catheter lock solution in Europe; nevertheless, there are other locking solutions. Although antibiotic-based lock solutions are effective in preventing CRBSI (26), the emergence of bacterial resistance could discourage their systematic use in the ICU (27). Ethanol locks could also be an attractive antimicrobial solution because of their activity against bacteria, fungi, and biofilms (28). Importantly, several lock solutions, such as ethanol, have been associated with adverse reactions (29) or can adversely affect catheter integrity (30). Different antimicrobial agents, such as those used for skin antisepsis (12), may have synergistic antimicrobial activity (31). The combining of several compounds is, therefore, a focus of research that has yielded promising results (32, 33).

The use of CLock was associated with less catheter colonization than the SOC. This observation is consistent with the anticoagulant and antibacterial (31, 34, 35) activity across a broad spectrum of microbes. Of note, thrombosis and bacterial growth within biofilm are closely related in the physiopathology of catheter-related infections (36).

The use of CLock was also associated with less catheter dysfunction. This observation is consistent with the anticoagulant properties of citrate through the chelation of calcium. Additionally, this observation supports that of the higher rate of catheter dysfunction found in the saline solution group than in the citrate group in a study by Hermite and colleagues (5). However, the reduction of catheter dysfunction in our study did not translate into longer catheterization durations, was highly physician dependent, and disappeared after propensity-score matching was performed.

The routine use of a 46.7% citrate solution by our experienced team as a catheter lock solution was not associated with higher mortality. However, the FDA sent out an urgent warning on 14 April 2000 reporting the risk of death when such a high concentration of citrate is infused into the blood of patients. This may be particularly relevant in the ICU population with acute renal failure and possibly acidosis, underscoring the need for close cardiac monitoring and compliance with the manufacturer recommendations.

Our study had several strengths. This study represented the third cohort (5, 8) and largest comparison employing individual data to investigate the risk of dialysis catheter infection when using citrate locking in the ICU; thus, this cohort is unique. The findings are biologically plausible and supported by *in vitro* (22, 28, 37) and *in vivo* (31, 35) studies. The effects of citrate on catheter-tip colonization, including the propensity-score-matched subcohort, which mimics "*post hoc*" randomization by balancing the recorded risk factors between groups, were consistent in our analyses. We are also aware of the limitations of the study. The study design compared CLock patients from one single institution, while comparator Cathedia patients were included by examining this institution plus 11 other institutions, in order to increase the power of the study. Nevertheless, the sensitivity analysis showed a limited effect of confounding when the analysis was restricted to patients in the same institution. The primary endpoint was catheter-tip culture without neutralizing broth, not CRBSI, which may limit the clinical relevance of our quasi-experimental study. Between the two time periods (2004 to 2007 for the Cathedia historical group and 2011 to 2012 for the Clock group), the effectiveness of the implementation of simple "bundle measures" to prevent the risk of CRBSI in patients admitted to intensive care units (38) could favor the CLock group, independently of the locking solution used. Maximal barrier precautions for catheter insertion and maintenance were already in use during the control period, chlorhexidine skin antisepsis was not available, avoidance of the femoral vein for vascular access was not relevant compared to avoidance of the jugular vein (7, 39), and exposures to central venous access were similar between the two periods. Moreover, the patient risk factors (2) and interventions that could increase or decrease the risk of catheter infection were prospectively monitored and standardized. Nevertheless, the possible increased use of ultrasound for catheter insertion from 2004 and 2012, as well as other unrecorded confounding factors, has not been taken into account.

This report may have important implications for future research. First, the robust association between intraluminal locking and the reduction of short-term catheter-tip colonization will aid in identifying the best composition of antimicrobial locks for use during interdialysis periods in the ICU setting (NCT01962116). Second, this strategy has the potential to reduce colonization. Particular attention should be focused on patient safety because a systemic leak of the locking solution could occur and may be masked or felt to be due to other etiologies and thus underreported.

In conclusion, citrate lock has the potential to improve acute hemodialysis safety in the ICU at reasonable cost. Additional experimental studies are required before the routine use of antimicrobial locks can be recommended for intermittent hemodialysis in the ICU setting.

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D.D.C. conceived of the study. J.-J.P. and D.D.C. designed the study. S.D., C.D., J.-P.M., B.M., and B. Souweine collected the data. J.-J.P. performed the statistical analysis and drafted the manuscript. We were all involved in the interpretation of the results and the critical revision of the manuscript.

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